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DIURETIN.

Read before the Pathological Section of the Chicago Academy of
Sciences, February 9, 1893.

BY

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BYTERIAN HOSPITALS, CHICAGO.

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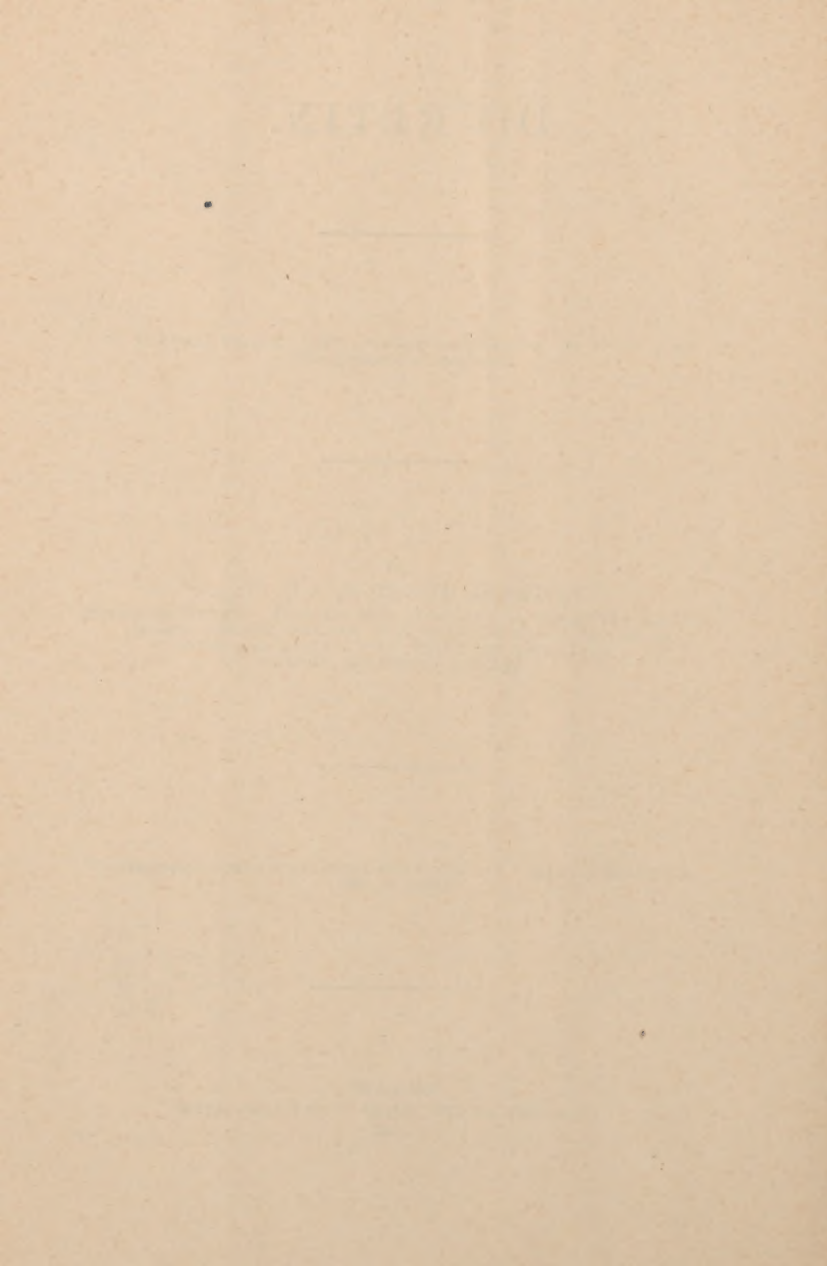
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The experiments of Schroeder reported in 1889, and confirmed by clinical observations made at Schroeder's suggestion, the same year by Gram, of Copenhagen, established the value of the alkaloid theobromine, a product of the seeds of *Theobroma cacao*, as a diuretic of great power, acting by direct stimulation of the renal epithelium and lacking in the unpleasant effects upon the nervous system, tinnitus, restlessness, insomnia and delirium, attributed to its homologue caffeine.

Gram, after trial of many compounds, overcame the disadvantage of the insolubility of the alkaloid by forming, by combination with salicylate of sodium, a double salt, sodium-theobromine-salicylate, which should contain at least 46.5 per cent. of the theobromine (Knoll's is said to contain 48 per cent.) and to which the name diuretin has been given. The therapeutic as well as commercial value depends upon its richness in theobromine. The compound occurs in the form of a white powder, soluble in less than its own weight of warm water, the solution remaining perfect on cooling. Pure diuretin should burn away without residue and should dissolve readily in soda solution. The daily amount administered—sixty to one hundred and twenty grains—is best given in divided doses of fifteen or twenty grains in

solution, pill or capsule. Exposure to the air permits of the absorption of carbonic dioxide, forming an insoluble compound, so that the drug should not be given in powder. With acids or syrups containing the fruit acids the theobromine is precipitated as a white powder. For solutions, therefore, water is the best vehicle, being flavored if thought advisable, to conceal the slightly sickish-bitter taste, with peppermint, wintergreen, or some other aromatic. Usually very little, if any, objection is made by the patient, because of its taste or any unpleasant effects.

Since Gram's paper in January, 1890, numerous observers have reported their experiences with diuretin. Hoffman, Koritschoner, and Kouindji-Pomerantz, published articles the same year, confirming Gram's and Schroder's position as to the remarkable diuretic effect of diuretin and its value in removing dropsical fluids. In Koritschoner's series of thirty-eight cases from the Vienna Hospital, excellent results were obtained in all, save five who came to the hospital practically *in extremis*. The cases successfully treated included dropsies from cardiac and renal diseases, from cirrhosis and cancer of the liver and from tubercular peritonitis. The only unpleasant effects noted were, occasionally vomiting and diarrhœa. Koritschoner, after a dosage of one hundred and fifty grains a day found palpitation and extremely anxious expression of countenance to follow. He produced this result both in a patient and in himself by this dose, which may therefore be looked upon as a maximum daily amount. The removal of the dropsical fluid in some cases was so rapid as to cause alarming collapse. Koritschoner, therefore, advises that the first doses should be small and gradually increased in size until the maximum dose is given, or the desired effect produced. In twenty-three of the thirty-eight cases the effect was

most excellent and it could only be said to be a failure in the five before mentioned cases, who entered the hospital beyond all hope of aid. In dropsies due to cardiac disease the result was most brilliant. Not only was no irritating effect produced on the renal epithelium, but in two cases of acute scarlatinal nephritis it caused prompt response in an increased activity of the kidney, and during its administration blood and casts disappeared from the urine.

Hoffmann made careful observations in Erb's clinic at Heidelberg, on seventeen cases of dropsy in which diuretin was given, and found the effect in dropsy of cardiac origin most remarkably satisfactory. In nephritis his results were not uniformly good, the best being obtained in the acute form. In cirrhosis of the liver the result was negative. Hoffman calls attention to the fact that the amount of urine passed under the influence of this drug, is in direct proportion to the amount of dropsical fluid present, while the specific gravity decreases with the increase in the amount of urine. It may be mentioned in this connection, that others, as Masius and Kress, have seen the specific gravity of the urine remaining high, owing to the greater amount of solids eliminated, notwithstanding the free diuresis. Contrary to Schroeder and Gram, who regarded diuretin as a purely renal stimulant, he finds as the result of careful watching of the pulse and heart, including the use of the sphygmograph, that under its influence the pulse becomes slower, fuller, stronger and more regular. The only unpleasant effects noted were, in a few cases, slight vomiting and diarrhoea, completely offset by the removal of the dropsical effusion, the improvemet in the heart's action, disappearance of bronchial catarrh, dyspnœa and insomnia.

Mme. Kouindji-Pomerantz, as the result of experimental and clinical investigations in the laboratory

of Dujardin-Beaumetz, reached the conclusions that diuretin, in daily doses of forty-five to seventy-five grains, is a diuretic of greater power, though less toxicity, than caffeine, with no action upon the nervous system and little effect upon the heart and producing no unpleasant urethral symptoms. It acts by stimulating the renal epithelium and is of great use in dropsies where this epithelium is not so hopelessly damaged as to be out of reach of all drugs. Patients do not become rapidly habituated to the drug. It should be given about three hours after meals to avoid unpleasant gastric symptoms supposed to arise from the action of the gastric juice upon the remedy, when it is taken with the food.

During 1891, reports from various sources, mostly German, appeared confirming, in the majority of instances, the conclusions of the observers of the year previous. Geisler had excellent results in the dropsy of valvular heart disease and in that of acute nephritis, while in myocarditis, chronic nephritis and hepatic cirrhosis the results were negative. Pfeffer in forty cases had good results in cardiac dropsy as well as in chronic nephritis and hepatic cirrhosis. His experience in acute nephritis was not so favorable. In some cases the amount of urine for twenty-four hours was six litres. Both Geisler and Pfeffer regard diuretin as a cardiac tonic and found after its use an increase in blood pressure. Schmieder and Siefert agree with others that the best results are obtained in cardiac dropsy and where there is general circulatory disturbance, though the latter obtained fairly good effects from diuretin in dropsy from portal vein obstruction.

In this country, Dr. Robert H. Babcock, of this city, was one of the first, if not the first, to report on the use of diuretin. He had excellent results, especially in dropsy dependent on valvular heart disease, and was convinced that, as Hoffman early asserted,

the remedy has an action upon the heart as well as upon the kidney. Laganà regards diuretin as the very best diuretic known, acting as well in acute as in chronic affections, having no deleterious influence on the kidney and more certain in its effects the more extensive the dropsy. He employed it in dropsy of heart disease, nephritis, hepatic cirrhosis and in acute and chronic pleurisy. Demme obtained good results in children in scarlatinal nephritis and in cardiac dropsy. Œdema in acute nephritis disappears, according to his observation, more rapidly under the influence of this drug than of any other.

Two unfavorable reports were made, one by Chmelnicku from Würzburg, and the other by Nickstaedt from Erlangen. The former found it of small benefit not alone in nephritis and portal vein dropsy, but in valvular diseases of the heart. In cardiac dilatation due to emphysema, however, the good effect was obtained. Nickstaedt by doses of sixty grains per diem produced in the healthy and the sick, malaise, headache, vomiting. He obtained less favorable results than with squills, acetate of potassium or calomel and thinks the use of the drug should be restricted to cases of dropsy where other diuretics fail.

In 1892 several reports have come in, among them an unfavorable one from Hare, of Philadelphia, and a favorable one from Frank of Prague. Hare's report is but preliminary and based on the observation of four cases. His cases are not the ones in which we should expect the most marked effects from the remedy when we consider that it is in cardiac dropsy that its influence is most pronounced and the effect shown on the urine is in proportion to the degree of dropsy. His first case was one of valvular disease with albumen, but no dropsy; no diuresis. Second, valvular disease, moderate œdema, moderate diuresis, which Hare attributes to digitalis rather than to diuretin. Third, general anasarca, albumen, no val-

vular disease; no increase in amount of urine. Fourth, enlarged prostate, concentrated urine, no œdema; no marked effect, though no accurate measurement of urine was possible.

Frank in von Jaksch's clinic, as the result of experience with thirty-four cases, regards diuretin as a superior diuretic in cases of dropsy and as a heart tonic, though inferior in this latter respect to digitalis. His best results were in cardiac dropsies, though in chronic nephritis, pericarditis, hepatic cirrhosis, he had fairly good results. In one case of chronic nephritis the effect was most remarkable. The patient passed, on the fifth day after taking the remedy, 3750 c.c. instead of 250 c.c. of urine. With this there was improved action of the hypertrophied and laboring heart and a rapid disappearance of the hydrothorax, hydroperitoneum, etc. Diuretin was stopped and digitalis begun and the amount of urine decreased at once. That the improvement in the heart's action was due to the effect of the remedy on the heart and not alone to the disappearance of the dropsical fluid, was proven, because in many of his cases "the pulse was good so long as the diuretin was continued, but became poor when it was stopped." Others have noted the bettering of the heart's action before the disappearance of the œdema, indicating a primary effect of the drug on the heart. In all of Frank's cases where any favorable result was obtained there was a six to fifteen fold increase in the urinary secretion. There was no renal irritation. In two cases albumen disappeared while the drug was being taken.

I desire to submit reports of the following cases:

Case 1.—Mrs. K., forty years of age, resident of Peoria, came under my care in 1891 with marked œdema of lower extremities, abdominal ascites, hydrothorax. The valvular disease of the heart, that was at the bottom of the trouble, had been previously unrecognized and consequently

untreated. The heart was hypertrophied and dilated, arrhythmic in its beat and a loud murmur could be plainly heard. This was made out later to be a mitral regurgitant murmur, it being impossible at first to locate definitely the valvular lesion on account of the tumultuous and irregular action of the heart. Mrs. K. suffered from intense dyspnoea and orthopnoea. This seemed a favorable case for treatment by rest and digitalis, which were prescribed and in addition, diuretin in fifteen grain doses four times a day was ordered. The effect was seen inside of twelve hours. Urine was passed in large amount every hour, day and night, and the abdominal ascites began to diminish at once. In two weeks all evidences of oedema had disappeared, the pulse was much more regular, and breathing became easy, the patient being able to lie down in bed without a sense of suffocation. Diuretin was discontinued and she returned home with instructions to continue the digitalis. In three weeks I had a letter from her asking for the other medicine (diuretin) as she was now passing a small amount of urine and was again becoming dropsical. Since then I have heard nothing from her.

Case 2.—Mr. K., from Ohio, fifty-two years of age, gives history of acute rheumatism nine years ago and of heart trouble ever since that date. Has taken largely of digitalis, yet during the last six months the heart's action has grown more irregular, dyspnoea more annoying and abdominal ascites and oedema of legs have reached an extreme degree. Entered the Presbyterian Hospital November 1, 1892.

Examination showed Mr. K. to be somewhat emaciated, jaundice fairly well marked, abdominal cavity tensely distended with fluid, legs oedematous, fluid in either pleural cavity. Mitral regurgitant murmur very loud, tricuspid systolic murmur, pulsation of jugulars. Urine, $\bar{3}$ xi, trace of albumen, casts.

November 3, tr. strophanthi gtt. vii t. i. d. and diuretin gr. xv q. i. d. ordered. Urine was passed in the next forty-eight hours, as Mr. K. said, in "enormous quantities." The first night he did not close his eyes in sleep, as he had to urinate every thirty minutes. The diuretin on November 6, was given in doses of eighty grains per diem. November 8, amount of urine over one gallon. In two weeks there was no oedema of the legs, the waist measure was lessened by nine inches, the heart was more regular and the enlarged liver, firm yet smooth, could be clearly made out extending two inches below the costal arch in the mamillary line. It pulsated synchronously with the heart and seemed to be the liver of passive hyperæmia of uncompensated heart dis-

ease and to give an explanation of the jaundice. After taking diuretin for three weeks in doses of eighty grains every day, Mr. K. had a slight chill, sudden rise in temperature to 103° F., nausea, though no vomiting. There was no sign of exacerbation of endocardial trouble, the urine showed the same amount of albumen as formerly and a few hyaline casts. The diuretin was stopped and in two days all unpleasant symptoms had disappeared. Twenty-four hours after stopping the diuretin there was a perceptible lessening in the amount of urine voided. After three days rest from the drug, its use was resumed and again the free diuresis began. The patient left the hospital December 1, with the abdominal ascites almost unnoticeable, with no œdema of the legs and with the heart beating with a fair degree of regularity and with good force.

Case 3.—H. C. male, 13 years of age. Had acute rheumatism four years ago and has had several attacks since. Has been treated for heart disease during these four years. Late in November 1892, I was called to see him and found a little œdema of the legs and a considerable amount of fluid in the abdomen. There was a loud mitral murmur, the heart was hypertrophied, liver enlarged; occasional vomiting. He now began to fill up with fluid quite rapidly and in a week his trouser's band failed by three inches to encircle the waist. He had to sit up in a chair one night in order to breathe easily. While continuing the capsule of digitalis, spartein and nuxvomica he had been taking, he also took now, ten grains of diuretin three times a day. He noticed the next day the increase in the amount of urine passed and in the frequency of micturition; he had to rise four or five times at night. In a week he was able to button his trousers and felt so well that he went to the theatre. After the ascites had disappeared the diuretin was stopped. In about ten days there was a reaccumulation of the fluid, which promptly disappeared a second time under the influence of diuretin. I had this patient buy the drug by the ounce, the druggist putting up a sample ten grain powder, the dose equivalent to the sample powder being measured out and taken in water. For about three days he took forty grains of diuretin daily, but as no perceptible benefit was apparent I dropped back to thirty grains. No unpleasant symptoms showed themselves during the exhibition of the drug.

Case 4.—Mr. B., 55 years of age, from Indiana. Came to Presbyterian Hospital Oct. 8, 1892, with typical history of alcoholic hepatic cirrhosis of some four years standing. Excessive ascites. Never had been tapped and desired to have fluid

removed by drugs rather than by operation. He was given salts every A.M. when necessary, and thirty grains of diuretin daily. Urine, before giving the drug was twelve to twenty ounces daily, after taking diuretin twenty to thirty ounces were passed. The daily dose was increased to 60 grs., without perceptible improvement. Dyspnea became so marked that I aspirated the abdomen October 28th, no bad effect following. October 30, diuretin was given in eighty grain doses. Nov. 2, there occurred a chill, temperature 103° F. pulse 128, vomiting and purging. I stopped the diuretin and in twenty-four hours all these unpleasant symptoms had disappeared. November 11, diuretin was resumed in forty grain doses, and on the 13th, in sixty grain doses. At 8 P.M. on this day the patient had a chill, nausea, diarrhoea, and rapid pulse as before. There appeared also in the left groin a purpuric lesion with a wide erythematous border, that extended half way to the knee and was somewhat tender. The diuretin was at once stopped, a wet boric acid dressing applied over the thigh and in two days the patient was about as before. The skin lesion, save the purpuric stain, promptly disappeared. I aspirated a second time November 18. He left for home November 30, in about the same condition as upon his entrance. I heard from him one month later; he had been tapped twice since leaving the hospital but had had no febrile attacks.

In a case of acute scarlatinal nephritis in a child of 11, the urine under thirty grains of diuretin a day has increased from eight ounces to thirty-one and the albumen has decreased from 50 per cent., by volume, to about 2 per cent. The case has only been under treatment for the nephritis for five days but at this writing the diuretin appears to be acting favorably.

It will be seen that in the case of cirrhosis of the liver the result was unsatisfactory, for though there was a slight increase in the amount of urine, no diminution in the dropsical fluid was perceptible. In the three cases of dropsy due to valvular heart disease the effect was eminently satisfactory, there following promptly, increased amount of urine, rapid diminution of dropsical fluid, strengthening of the heart's action with slowing and regulating of its

rapid and irregular beat, improvement in appetite and disappearance of dyspnoea and cyanosis.

In these cases I administered at the same time a cardiac tonic, strophanthus in case 2, and digitalis in the others. In case 1, a part of the improvement can, perhaps, justly be attributed to the digitalis, as this remedy had never before been administered; but the free diuresis and rapid disappearance of dropsy were far beyond anything I have ever seen from ten drops of the tincture of digitalis three times a day, and after stopping the diuretin fluid rapidly reappeared in the abdomen. In cases 2 and 3, digitalis and various other heart tonics had been taken almost constantly, in the one case for nine years and in the other for four. In the latter case, in fact, I had the patient continue with exactly the same capsule (pulv. digitalis, spartein sulph., ext. nuc. vom., etc.), he had been taking for many weeks and during the taking of which, the fluid had accumulated in the abdomen. In all three of these cases, too, the diuretin was stopped and within forty-eight hours there was a diminution in the amount of urine and in cases 1 and 3, a reaccumulation of dropsical fluid. Return to diuretin produced the same favorable consequence as at first. The effect of the diuretin cannot, therefore, be questioned. It has seemed to me an advantageous method of administering the drug to combine it, in these heart cases especially, with digitalis or some other heart tonic. In my cases in this way, a moderate dose of sixty grains a day produced all the results that could be asked. I find that Frank regards this as an excellent method, and Demme, in the case of a child, gave first digitalis and then diuretin after the effect of the former drug on the heart was manifest. The unfavorable consequences, vomiting, slight chill and fever and diarrhoea, disappeared promptly on stopping the remedy. These effects were possibly cumulative, the drug having

been administered in the one case for three weeks and in the other for eight days, in either case in increasing doses. Cumulative effect is not noted by other observers and it may be that the effects noted by me are no more than the vomiting, diarrhœa, etc., spoken of by others. The skin lesion which appeared in case 4, is different from anything I have seen noticed. Its occurrence at the time of administration of the maximum dose for this patient, as evidenced by the gastro-intestinal symptoms and its rapid disappearance upon stopping the drug, lead me to regard it as due to the remedy and not solely accidental. Demme, in a ten years old child with amyloid disease of the liver, spleen and kidney, produced by diuretin a rash resembling that of measles. Ninety grains were given in the course of four days. Profuse diarrhœa occurred at the same time the rash appeared. I find no other record of skin lesion due to the ingestion of the drug.

Since writing this article I have had kindly placed at my disposal by Dr. A. E. Halstead of this city, the notes of four cases occurring in his practice, in which diuretin was employed. An abstract of these notes is here appended.

Case 1.—Mrs. E. G., mitral regurgitation; chronic parenchymatous nephritis with acute exacerbation. Total urine for 24 hours $\bar{5}v$; vomiting, twitchings, slight coma. Given calomel gr. $\frac{1}{4}$, and diuretin gr. x, every two hours, and in addition a hot bath. Gradual improvement. At end of one week, urine $\bar{5}xxiv$ daily, no vomiting, mind clear.

Case 2.—J. G., mitral stenosis and regurgitation, chronic nephritis. General anasæra, severe dyspnœa; amount of urine secreted in 24 hours, $\bar{5}xv$. Treatment, magnesium sulphate, $\bar{5}ss$. A.M. and P.M. tr. digitalis mx., t. i. d., and diuretin gr. x, every four hours. On the second day urine $\bar{5}xl$. At end of week $\bar{5}cxx$. At end of two weeks entire disappearance of œdema, dyspnœa, etc.

Case 3.—A. H., aged 83. Diagnosis. Arterio-capillary fibrosis; contracted kidney, secondary mitral insufficiency. General anasæra, ascites, hydrothorax. Under diuretin, pulse harder, dyspnœa greater, headache and vertigo marked.

Diuretin discontinued and jalap, cream of tartar, and later, nitro-glycerin substituted. Under latter treatment amelioration of all unpleasant symptoms.

Case 4.—Miss M., age 17. Chronic nephritis with acute exacerbation; uræmic prodromes marked. Urine \S viii. Given digitalis, diuretin and calomel. Urine at end of two weeks \S L.

In these cases of Dr. Halstead's, it will be noticed that a favorable result was obtained in three, while in the case of capillary fibrosis there seemed to be an increase of blood pressure and exacerbation of all the unpleasant features of the disease. The most marked result, in case 2, was in a patient suffering from valvular disease with excessive dropsical transudation, apparently the kind of case in which we are to expect the best effects. While all the benefit derived in these cases cannot be ascribed to diuretin, for other remedies were freely combined with it, Dr. Halstead assures me that from his observation of the cases diuretin deserves the great share of the credit.

That diuretin properly employed, is a remedial agent of great value, must I think, be admitted by all. While the exact pathological conditions that call for its exhibition cannot as yet be specifically stated and disappointing failures will therefore attend its misapplied use in many cases where too much will be hoped for, yet, a study and comparison of the results of the various observers who have employed this remedy in the past three years, yield facts from which certain conclusions can be drawn.

My study of the literature of diuretin, and experience with the remedy seem to warrant the following deductions:

1. Diuretin is a diuretic acting by direct stimulation of the renal epithelium and best suited to cases in which there is general dropsical effusion.

2. It is the best medicinal remedy for removing dropsical fluid due to valvular disease of the heart,

after digitalis and pure cardiac tonics have failed.

3. It can be advantageously combined with digitalis and pure cardiac tonics.

4. It probably has a direct effect upon the heart as well as upon the kidney, slowing and strengthening its action and improving its rhythm. (This is disputed by some; viz.: Cohnstein, *Ueber den Einfluss der Theombromine, etc., auf den arteriellen Blutdruck*. Inaug-Diss., Berlin, 1892).

5. Diuretin has oftentimes a beneficial effect in other circulatory diseases with dropsy, as myocarditis, pericarditis, aneurism, arterio-sclerosis. Its action is here more uncertain than in valvular disease.

6. In the dropsy of nephritis it can be used without danger of irritating the kidney, the effects in acute nephritis being more certain than in chronic nephritis. Where the renal epithelium has undergone too extensive degeneration, the drug may fail to act.

7. In the dropsy of portal obstruction, and especially of cirrhosis of the liver, it usually fails to give good results.

8. It occasionally causes nausea, vomiting, diarrhoea, palpitation, headache and slight fever; rarely, skin eruptions follow its use.

9. The maximum daily amount that can be given with safety is 150 grains; the average daily amount is 50 to 120 grains, given in divided doses. When combined, in heart cases, with cardiac tonics, smaller doses of diuretin can be employed.

10. It should be given in solution in water or milk, or in pill or capsule, without acids and by preference between meals.

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